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PATENT SPECIFICATION

(11) 1 565 056

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(21) Application No. 48809/76 (22) Filed 23 Nov. 1976
(31) Convention Application No. 636009
(32) Filed 28 Nov 1975
(31) Convention Application No. 636010
(32) Filed 28 Nov. 1975 in
(33) United States of America (US)
(44) Complete Specification published 16 April 1980
(51) INT CL³ C07D 213/78 A61K 31/44 (C07D 213/78 295/00 401/02 413/02)
(52) Index at acceptance

C2C 1341 1492 1530 1531 1532 1562 1626 20Y 215 220 226 227 22Y 246 247 250 251 252 253 255 25Y 271 272 280 28X 290 29X 29Y 304 305 30Y 311 313 314 31Y 322 326 32Y 334 337 338 342 34Y 351 352 355 35X 360 361 362 364 366 367 368 36Y 37X 386 388 431 436 43X 440 485 490 491 500 502 50Y 55X 574 579 584 620 623 624 625 628 62X 62Y 633 634 652 656 65X 662 672 675 676 678 68Y 694 697 699 69Y 731 73Y 761 762 776 77X 802 80Y AA BB BJ KF KP KQ LD MB MC MD NR TT UJ WB YX ZJ ZK ZM

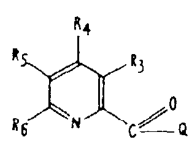
(19) THE PATENT OFFICE LONDON

(54) PICOLINIC ACID DERIVATIVES AND PROCESSES FOR THEIR PREPARATION

(71) We, SCHERICO LTD., of Topferstrasse 5, Lucerne, Switzerland, a body corporate constituted under the Laws of Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

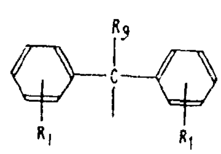
This invention relates to valuable therapeutically active novel picolinic acid derivatives, to compositions containing these compounds, to processes for making these compounds and compositions, and to methods of using them. In particular the novel compounds are useful anti-acne agents.

One aspect of this invention relates to the novel picolinic acid derivatives of the general formula



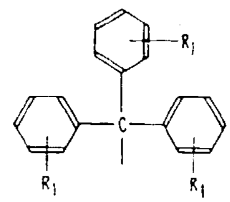
(1)

and the pharmaceutically acceptable salts thereof, wherein Q is hydroxy, alkoxy, cyanoalkoxy, glyceryloxy, $—NR_7R_8$, $—O—$alkylene$—NR_7R_8$ or $—NR_7—$alkylene$—OH$; R_7 and R_8 which may be the same or different are hydrogen or alkyl or R_7 and R_8 together with the amido nitrogen atom may form a 5 to 7 membered heterocyclic ring which may contain a second heteroatom, being oxygen or nitrogen; R_3 is hydrogen, a diphenylmethyl group of the general formula



(II)

or a triphenylmethyl group of the general formula



(III)

wherein R_1 is hydrogen, halogen, hydroxy, alkyl, alkoxy, trifluoromethyl or phenyl and R_2 is hydrogen or lower alkyl; and when R_5 is hydrogen, R_3 and R_6 are hydrogen and R_4 is a diphenylmethyl group of the general formula (II) defined above; and when R_5 is the diphenylmethyl group (II), R_4 and R_6 are hydrogen and R_3 is hydrogen, lower alkyl or a diphenylmethyl group of the general formula (II) defined above; and when R_5 is the triphenylmethyl group (III), R_3, R_4 and R_6 are hydrogen or one of R_3, R_4 and R_6 is lower alkyl the other two being hydrogen.

The substituents R_1 in a compound of formula (I) can be identical or different from each other.

As used herein the term "alkyl" means a straight, branched chain or cyclized alkyl having preferably up to 12 carbon atoms. The term "alkoxy" means a group wherein a straight, branched chain or cyclized alkyl having preferably up to 12 carbon atoms, is bonded to an oxygen atom by a single bond. When such terms are modified by the term "lower" than such radicals contain up to six carbon atoms. Representative of the alkyl and alkoxy groups are methyl, ethyl, propyl, n-butyl, t-butyl, octyl, dodecyl, isopropyl, cyclopropyl, cyclopentyl, cycloheptyl, cyclooctyl, methoxy, ethoxy, propyloxy, *n*-butyloxy, t-butyloxy, octyloxy, dodecyloxy, isopropyloxy, cyclopropyloxy, cyclopentyloxy, cycloheptyloxy and cyclooctyloxy, with the lower alkyl and lower alkoxy groups being preferred.

The term "—O—alkylene—NR_7R_8" which is sometimes also described herein as "aminoalkyloxy", represents an alkylene group consisting of a divalent straight, branched or cyclized hydrocarbon radical having preferably up to 12 carbon atoms, which is between an oxygen atom and the NR_7R_8 group. Preferably, the alkylene moiety has up to six carbon atoms. Among the preferred "—O—alkylene—NR_7R_8" groups are: aminoethoxy, aminopropyloxy, aminovaleryloxy, mono and dialkylaminoethoxy, mono and dialkylaminovaleryloxy, piperidinoethoxy, morpholinoethoxy, piperazinoethoxy, pyrrolidinoethoxy, morpholinopropyloxy, morpholinovaleryloxy and piperazinoisopropyloxy.

Examples of groups represented by "NR_7R_8" are amino, mono and dialkylamino, morpholino, pyrrolidino, piperidino and piperazino.

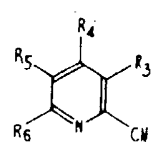
In view of the foregoing definition of the terms "NR_7R_8" and "O—alkylene—NR_7R_8", the definition of the terms "NR_7—alkylene—OH" and "O—alkylene—CN" (cyanoalkoxy) are obvious.

Exemplary of the salts of the picolinic acids of formula I, i.e. wherein "Q" represents hydroxy, are those formed with alkali metals, alkaline earth metals (e.g. formed with the hydroxides, carbonates or bicarbonates thereof) and non-toxic organic bases such as amines (e.g. triethylamine, N-methyl glucamine) and alcoholamines (e.g. diethanolamine).

The invention further provides a pharmaceutical compositions comprising as active ingredient a compound of general formula (I) or a pharmaceutically acceptable salt thereof in association with a suitable pharmaceutical carrier. Also the present invention provides a process for the preparation of a pharmaceutical composition which comprises bringing a compound of general formula (I) or a pharmaceutically acceptable salt thereof into a form suitable for therapeutic administration, for example by admixing said compound with a suitable pharmaceutical carrier.

The novel picolinic acid derivatives of this invention can be prepared by standard methods such as described below.

A. Compounds of the general formula (I), wherein Q is hydroxy, the other substituents being defined as above, can be prepared by hydrolysis of the corresponding nitrile (V).

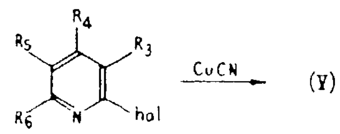


(V)

The nitrile may directly be converted to the acid (I) via an intermediate alkali metal salt which is then converted to its desired acid form. Standard purification through salt formation and hydrolysis techniques well known to those of ordinary skill in the art may be employed. Preferably the nitrile is reacted in an organic solvent such as glycols e.g. ethylene glycol or propolene glycol, with an aqueous solution of potassium hydroxide. The reaction may be performed at elevated temperature e.g. at reflux temperature, over a long period of time such as about 80 hours.

For the preparation of compound (I), wherein R_5 is a triphenylmethyl group (III) defined above, the starting material can be prepared as follows:

Reaction Scheme 1



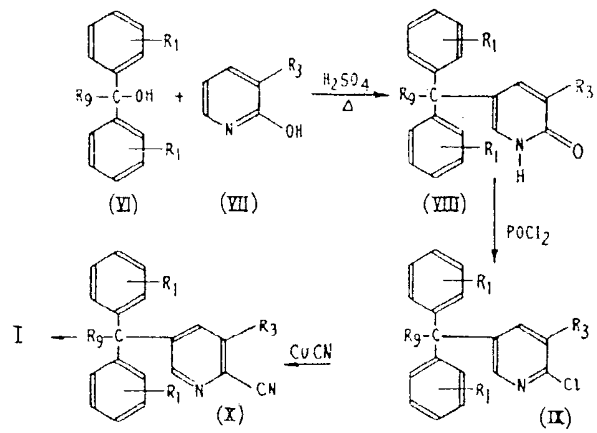
(IV)

In formula (IV) and (V), R_3, R_4 and R_6 are as defined above, R_5 is the triphenylmethyl group (III) and hal is halogen (preferably chloro or bromo). The halogenopyridines (IV) may be prepared according to the Journal of the American Chemical Society *71*, 387—390 (1949). By standard techniques, such as by heating compound (IV) and cuprous cyanide at elevated temperatures, preferably in the presence of an inert organic solvent, for 2 to 10 hours, the nitrile (V) is formed. For example, the reaction is very smoothly effected in refluxing dimethylformamide in from 4 to 6 hours. Isolation of the nitrile (V) may be accomplished by standard extraction techniques after the reaction mixture has been quenched; preferably by utilization of a non-water miscible solvent, e.g. benzene, toluene or ethyl ether. The crude nitrile (V) may directly be used in the above described process A.

The compounds of this invention having a lower alkyl group at the 3-position may be prepared as follows: A 2-amino 3-lower alkyl pyridine (e.g. 2-amino-β-picoline) is reacted with nitrous acid to yield the corresponding 3-lower alkyl pyridone. The latter compound may be converted to the corresponding 3-lower alkyl 5-triphenylmethyl picolinic acid by the procedure set forth hereinabove.

The preferred reaction sequence by which the compounds having a diphenylmethyl group (II) at the 5-position may be prepared is initiated by the reaction wherein a benzhydrol (VI) is condensed with a 2-hydroxypyridine (VII) to produce a substituted diphenylmethyl pyridone (VIII). This condensation is effected by heating a mixture containing equimolar quantities of the reactants within the temperature range of 225°C to 275°C (preferably about 245°C) in the presence of a strong acid, such as, for example, sulfuric acid. The pyridone (VIII) is treated with a phosphorous oxyhalide reagent, e.g. phenylphosphonic dichloride, at an elevated temperature thereby forming the corresponding 2-halogeno pyridine (IX). The 2-halogeno compound (preferably 2-chloro or 2-bromo compound) is converted to its 2-cyano analog (X) by conventional means (e.g. as described above). The 2-cyano analog is then hydrolyzed to the corresponding substituted diphenylmethyl picolinic acid (I) as described above. The foregoing reactions are depicted by the following flow diagram:

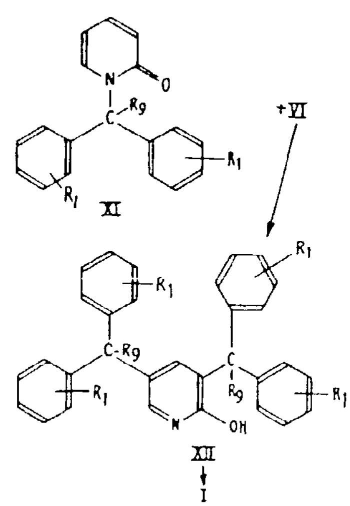
Reaction Scheme II



In the process described by the sequence set forth above, R_1, R_3 and R_9 are as defined for formula I.

In the preferred method for preparing the compounds (I), wherein R_3 and R_5 represent a diphenylmethyl group (II), 2-hydroxypyridine is reacted with a benzhydrol under substantially the same reaction conditions described for the preparation of compounds (VIII) in Reaction Scheme II, except the reaction is effected at from 150° to 200° to favor the condensation of the benzhydrol at the 1-position (i.e. on the nitrogen atom of the pyridine moiety). When a second mole of substituted benzhydrol is subsequently condensed with the first condensation product (XI), the reaction is effected at a temperature in the range of from 225° to 275°. This reaction causes migration of the first benzhydryl moiety from the nitrogen atom, and the concomitant condensation of a second benzhydryl moiety to produce an appropriately substituted 3,5-[bis-(diphenylmethyl)]-2-hydroxypyridine (XII). The product is converted to the corresponding 3,5-[bis-(diphenylmethyl)]-picolinic acid by substantially the same series of reactions described in Reaction Scheme (II). This reaction is depicted in

Reaction Scheme III



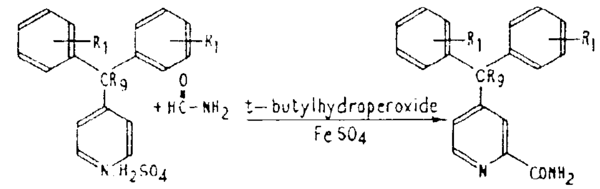
wherein R_1 and R_9 are as defined above.

B. Compounds of the general formula (I), wherein Q is NH_2, the other substituents being defined as above, can be prepared by hydrolysis of the corresponding nitrile (V) under mild conditions. In the description of process A the nitrile (V) is

defined, as well as its preparation is described). Preferably this hydrolysis is performed by heating the nitrile (V) with potassium hydroxide in a mixture of water and an organic solvent such as for example methanol, ethanol, propanol and isopropanol.

C. Compounds of formula I, wherein R_1 is a diphenylmethyl group (II) (defined above) and Q is NH_2, the other substituents being defined as above, can be prepared by reacting a corresponding 4-benzhydrylpyridinium sulfate salt (XIII) or 4-benzhydrylpyridine in the presence of sulfuric acid with formamide in the presence of ferrous sulfate and a peroxide, preferably *t*-butylhydroperoxide, to form the corresponding 4-benzhydryl picolinamide (XIV).

Reaction Scheme IV

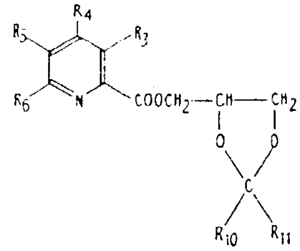


XIII XIV

wherein R_1 and R_9 are as defined above.

To prepare the compounds of this invention wherein R_9 represents a lower alkyl radical, it is preferable first to alkylate a 4-diphenylmethyl pyridine and then follow the series of reactions set forth in Reaction Scheme (IV). The alkylation can be effected in an inert solvent by reaction with a lower alkyl halide in the presence of sodium amide and excess ammonia, with ferric nitrate being present in catalytic quantities according to standard techniques known in the art.

D. Compounds of formula I, wherein Q is glyceryloxy can be prepared by the hydrolysis of an alkylidenedioxypropyl ester of an appropriately substituted picolinic acid (XV),



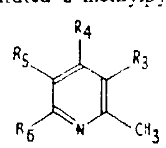
(XV),

wherein R_3, R_4, R_5 and R_6 are defined as above and R_{10} and R_{11} are lower alkyl, containing up to 6 carbon atoms.

Hydrolysis of (XV) to yield the desired glyceryl ester is usually effected by conventional techniques, such as by heating the intermediate in the presence of an acid, for example, by heating the intermediate in dilute acetic acid until the reaction is substantially complete and isolating the glyceryl ester by means known to the art.

The alkylidenedioxypropyl ester (XV) is generally prepared by transesterification wherein a reactive alkyl ester of the appropriately substituted picolinic acid, such as a cyanomethyl ester is transesterified by a cyclic acetal of glycerol. The transesterification is generally effected by heating the reactive ester with the cyclic acetal of glycerol in the presence of catalytic amounts of a tertiary amine catalyst, such as triethylamine at temperatures in the range of 80°—200°C, about 100°C being preferred. Due to the nature of the transesterification it is advantageous to employ a large excess of cyclic acetal to drive the reaction to completion.

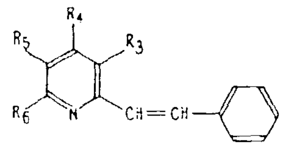
E. Compounds of formula (I), wherein Q is hydroxy can also be prepared by oxidation of an appropriately substituted 2-methylpyridine of the formula (XVI)



(XVI),

wherein R_3, R_4, R_5 and R_6 are as defined above. Preferably the oxidation is performed by means of selenium dioxide. The reaction is performed in an organic solvent, such as for example pyridine containing water at reflux temperature of the reaction mixture. The oxidation can also be performed with potassiumpermanganate, provided R_5 is the triphenylmethyl group and R_3, R_4 and R_6 are hydrogen, preferably in water.

F. Compounds of formula (I), wherein Q is hydroxy can also be prepared by oxidation of an appropriately substituted 2-styrylpyridine of formula (XVII)



(XVII),

wherein R_3, R_4, R_5 and R_6 are defined as above. Preferably the oxidation is performed by means of potassiumpermanganate in acetone, at temperatures of $-5°C$ to $-15°C$, or by means of selenium dioxide.

If desired a compound of formula (I) obtained by any one of the above processes can be subjected to at least one of the following aftertreatments:

i) Transformation of the compound into its salt. The salts of compounds (I), wherein Q is hydroxy may be prepared by reacting the acid with an excess of base in a suitable solvent.

ii) Setting free the compounds (I) from their salts.

iii) Conversion of a compound (I), wherein Q is hydroxy into the compound (I), wherein Q is alkoxy, cyanoalkoxy, glyceryloxy or —O—alkylene—NR_7R_8. For the preparation of the cyanomethylester this conversion is usually effected by treating the acid at an elevated temperature with a halegenoacetonitrile in the presence of an acid acceptor, such as triethylamine. The reaction is, advantageously, effected in a non-reactive organic solvent such as acetone or methyl ethyl ketone. The reaction is allowed to proceed for from 5 to 20 hours, the reaction mixture is cooled and filtered. The filtrate is concentrated to a residue and triturated with water to yield the desired cyanomethyl ester. The cyanomethyl ester is a key intermediate from which nearly all of the compounds having the various Q substituents may be prepared.

The other cyanoalkylesters can be prepared analogously.

iv) Conversion of a compound of formula (I), wherein Q is cyanoalkoxy (the alkoxy group containing up to 6 carbon atoms), wherein the cyano group is attached to the C-atom of position 1 (i.e.

$$\begin{array}{c} CN \\ | \\ —O—CH \end{array}$$

alkyl), preferably cyanomethyloxy into a compound of formula (I) wherein Q is alkoxy, —NR_7R_8, —O—alkylene—NR_7R_8 or —NR_7—alkylene—OH by transesterification and/or amidation techniques.

For example, subjecting the cyanomethyl ester to a conventional base catalyzed alcoholysis permits the alcohol to replace the cyanomethyl moiety thereby yielding an alkyl ester derivative. In like manner, by treating the cyanomethyl ester with a dialkylamine at an elevated temperature, the corresponding dialkylamide may be prepared. Of course, in those instances wherein the transesterification process is designed to produce an amine having a reactive hydrogen, the amine groups are first protected (e.g. by standard benzylation procedures) and subsequent to the transesterification, protective groups (e.g. benzyl), are readily cleaved by standard techniques well known in the art. Similarly, when Q represents a hydroxyalkylamine, the terminal hydroxy moiety must first be protected e.g. with hydroxy (ether) protecting group and then following transesterification the protecting group removed. These procedures are conducted according to techniques well known in the art.

v) Conversion of a compound of formula (I) wherein Q is hydroxy into a compound of formula (I) wherein Q is alkoxy or —NR_7R_8 by standard esterification and amidation procedures.

vi) Conversion of a compound of formula (I) wherein Q is other than hydroxy especially NR_7R_8, preferably NH_2 by hydrolysis under preferably acidic conditions, into a compound (I) wherein Q is hydroxy.

Acne is a common inflammatory disease in areas where sebaceous glands are

largest, most numerous, and most active. It is characterized by the appearance of comedones, pustles, papules, inflammed nodules, and in extreme cases infected sacs. In the more inflammatory types of acne, *Corynebacterium acnes* and *Staphylococcus albus* are usually among the infecting organisms. It is believed that these organisms aggravate the existing inflammatory condition by releasing enzymes (lipase) which break down the lipid in the sebum with the concomitant release of irritating fatty acids. Thus, an effective anti-acne agent ought be one which can prevent or substantially reduce the breakdown of lipid in the sebum thereby exerting an anti-inflammatory effect upon the skin. Ideally, the anti-acne agent should be effective topically in order to minimize the advent of untoward side effects which may occur during systemic treatment. For instance, the more frequently used anti-acne agents, e.g. the tetracyclines, are believed to be casually related to side effects which appear with the long term systemic treatment usually required in treating acne. These adverse effects include gastrointestinal irritation, photosensitivity reactions, dizziness, nausea and vomiting. Thus, there is need for effective topically applied anti-acne agents. The compounds of this invention fill such a need, being useful in the treatment and alleviation of acne.

When tested *in vitro* by a slightly modified version of the test procedure described by A. Shalita and V. Wheatley, in J. Invest, Dermatol. *54*, 413 (1970), the compounds of this invention were shown to substantially inhibit the formation of free fatty acids from triglycerides by bacterial lipases, including those formed by *Corynebacterium acnes*. The free fatty acids produced were assayed by the automated colorimetric method of C. Dalton and C. Kowalski as described in Clinical Chem. *13*, 744 (1967). Further, the test results clearly demonstrate that the anti-lipase activity of the compounds of this invention is substantially greater than that of hexachlorophene, or that of tetracycline. Additionally, neither hexachlorophene nor tetracycline exhibit substantial *in vivo* topical activity whereas the compounds of this invention do. Moreover, the instant compounds are substantially devoid of overt skin irritation upon repeated topical administration. They also exhibit little systemic toxicity following repeated topical application or upon systemic dosing *via* oral or intraperitoneal administration.

As mentioned, the compounds of this invention are effective antibacterial agents, particularly against *Corynebacterium acnes* and *S. albus*. Additionally, the compounds of this invention are effective against other gram-positive organisms and they also are antitrichomonal; they being particularly effective against *T. vaginalis*. As such, the compounds may be used in the conventional manner for treating gram-positive infections and for treating trichomonal infections. Potency assays and formulations for such uses utilize standard techniques.

For the treatment of acne the compounds of this invention are administered topically in pharmaceutical compositions having the conventional excipients. The compositions may be in the form of lotions, creams, aerosols and ointments. In these compositions, the active compound is present in the range of from 0.5% to 10% preferably 1.5—5% by weight, administration being from 2 to 5 times daily.

As is generally the case wherein a family of compounds exhibits a particular utility, certain members are preferred over others. In the present invention, a preferred group of compounds are those compounds of formula I defined above wherein Q is hydroxy, alkoxy, cyanoalkoxy, glyceryloxy or NH_2, said alkyl and alkoxy groups having 1 to 12 carbon atoms, R_2 is hydrogen, a diphenylmethyl group of the general formula II or a triphenylmethyl group of the general formula III, wherein R_1 is hydrogen, halogen, hydroxy, alkyl, alkoxy, said alkyl and alkoxy groups having 1 to 6 carbon atoms, trifluoromethyl or phenyl and R_6 is hydrogen or alkyl containing 1 to 6 carbon atoms, and wherein when R_2 is hydrogen, R_3 and R_6 are hydrogen and R_4 is a diphenylmethyl group of the general formula (II) defined above, and when R_2 is the diphenylmethyl group (II), R_4 and R_6 are hydrogen and R_3 is hydrogen, alkyl containing 1 to 6 carbon atoms or a diphenylmethyl group of the general formula (II) defined above, and when R_2 is the triphenylmethyl group (III), R_3, R_4 and R_6 are hydrogen or one of R_3, R_4 and R_6 is alkyl containing 1 to 6 carbon atoms, the other two being hydrogen, especially compounds wherein Q is hydroxy, alkoxy containing 1 to 3 carbon atoms, OCH_2CN, NH_2 or glyceryloxy and R_1 is hydrogen, halogen or phenyl.

Of particular interest is the group of compounds of formula I wherein Q is hydroxy, alkoxy containing 1 to 3 carbon atoms, OCH_2CN, glyceryloxy or NH_2, R_2 is hydrogen, a diphenylmethyl group of the general formula II or a triphenylmethyl group of the general formula (III), wherein R_1 is hydrogen, chloro or phenyl and R_6 is hydrogen, methyl or ethyl, and when R_2 is hydrogen, R_3 and R_6 are hydrogen and R_4 is a diphenylmethyl group of the general formula (II) defined above; and when R_2 is the diphenylmethyl group (II), R_4 and R_6 are hydrogen and R_3 is hydrogen or the

diphenylmethyl group (II), and when R_5 is the triphenylmethyl group (III), R_3, R_4 and R_6 are hydrogen or one of R_3, R_4 and R_6 is lower alkyl the other two being hydrogen; especially compounds wherein R_1 is hydrogen or chloro.

From these compounds those are of particular interest, wherein Q is hydroxy or isopropoxy, R_5 is the diphenyl group (II) or triphenyl group (III), wherein R_1 and R_2 are hydrogen and when R_5 is the diphenylmethyl group (II), R_4 and R_6 are hydrogen and R_3 is hydrogen or the diphenylmethyl group (II) and when R_5 is the triphenylmethyl group (III) R_3, R_4 and R_6 are hydrogen.

The most preferred compounds are 5-diphenylmethyl picolinic acid, 3,5-bis(diphenylmethyl) picolinic acid, 5-triphenylmethyl picolinic acid isopropyl ester, particularly 5-tritylpicolinic acid, 5-[α-(4-chlorophenyl)-benzyl]-picolinic acid, 5-triphenylmethyl picolinic acid cyanomethyl ester, 5-triphenylmethyl picolinic acid methyl ester, 5-triphenylmethyl picolinic acid glycerolester and salts of the compounds being able to form salts especially their diethanolamine salts.

The following Examples A to E are directed to topical formulations in which the compounds of this invention may be utilized to elicit an anti-acne response. The formulations are prepared by methods known in the art using the active compound in the form of a solid of particle size below 5μ.

From the compounds of formula I containing a pyridine ring substituted by a lower alkyl group, those are preferred, wherein this lower alkyl group is in position 3, such as for example 3-methyl-5-(triphenylmethyl)-picolinic acid.

EXAMPLE A

Ointment	mg/gm
5-tritylpicolinic Acid diethanolamine salt	20.0
Propylene Glycol, USP	40.0
Mineral Oil, USP	50.0
White Petrolatum, USP to make	1.0 g.

EXAMPLE B

Ointment	mg/gm
Glyceryl (5-Triphenylmethyl)-picolinate	20.0
Propylene Glycol, USP	40.0
Stearyl Alcohol, USP	50.0
Polyethylene Glycol 400, USP	600.0
Polyethylene Glycol 4000, USP to make	1.0 g

EXAMPLE C

Gel	mg/gm
5-tritylpicolinic Acid	20.0
Propylene Glycol, USP	300.0
Polyethylene Glycol, 400 USP	660.0
Butylated Hydroxytoluene	5.0
*Carbopol 940P	15.0
Titanium Dioxide, USP	10.0
Sodium Hydroxide, USP	0.7

* "Carbopol" is a Registered Trade Mark

EXAMPLE D

Cream	mg/gm
5-tritylpicolinic Acid	20.0
Stearic Acid, USP	60.0
Glyceryl Monostearate, Cosmetic	100.0
Propylene Glycol, USP	50.0
Polyoxyethylene Sorbitan Monopalmitate, Cosmetic	50.0
Sorbitol Solution, USP	30.0
Benzyl Alcohol, N.F.	10.0
Purified Water, USP to make	1.0 gm.

EXAMPLE E

Glycol Ointment	mg/gm
5-tritylpicolinic Acid diethanolamine salt	20.0
Propyl Glycol Monostearate	20.0
Propylene Glycol, USP	100.0
White Wax USP	60.0
White Petrolatum qs to make	1.0 gm.

The preparation of the compounds of formula (I) is illustrated by the following specific examples:

EXAMPLE 1

5-(Triphenylmethyl)-Picolinic Acid

A. 2-Bromo-5-(Triphenylmethyl)-Pyridine

Heat at reflux for 3 hours a mixture of 50.6 g. 5-(triphenylmethyl)-2-pyridone and 171 g. phosphorous oxybromide. Pour onto ice and stir on steam bath to decompose excess phosphorous oxybromide. Filter, dry solids, and triturate the product with benzene and ethanol to obtain the product of this example, m.p. 273—276°.

B. 5-(Triphenylmethyl)-Picolinic Acid

Heat at reflux a mixture of 46.9 g 2-bromo-5-(triphenylmethyl)-pyridine and 21.5 g cuprous cyanide in 450 ml. dimethylformamide for 5 1/2 hr. Pour onto a mixture of ice and 200 ml. ethylene diamine, extract with benzene, dry the benzene extracts, and concentrate. The crude, viscous 2-cyano-5-(triphenylmethyl)-pyridine may be purified by crystallization from acetonitrile to yield a product melting at about 176°—179° or the compound may be converted directly to the acid via the potassium salt by heating it at reflux with 20 g potassium hydroxide pellets in 120 ml. H_2O and 400 ml. ethylene glycol for 15 hr. Filter the hot solution, cool the filtrate which precipitates the potassium salt of the acid. Filter the salt and wash with ethylene glycol, suspend in water, acidify and heat for 1 hr. Filter the acid, dry and recrystallize from acetonitrile, m.p. 215—217°.

Additional acid is obtained by concentrating the ethylene glycol filtrate of the potassium salt and acidifying.

In a similar manner, subject an equivalent quantity of the following compounds (which can be prepared as described in step A of this example) to the process set forth above.

2-bromo-3-methyl-5-(triphenylmethyl)-pyridine,
2-bromo-5-[(4-biphenyl)diphenylmethyl]-pyridine,
2-bromo-5-[(4-chlorophenyl)diphenylmethyl]-pyridine,
2-bromo-5-[tris-(4-chlorophenylmethyl)]-pyridine,
2-bromo-5-[(4-methylphenyl)diphenylmethyl]-pyridine,
2-bromo-5-[bis-(4-fluorophenyl)phenylmethyl]-pyridine,
2-bromo-5-[(4-methoxyphenyl)diphenylmethyl]-pyridine,
2-bromo-5-[(4-trifluoromethylphenyl)diphenylmethyl]-pyridine,
2-bromo-3-methyl-5-[(4-trifluoromethylphenyl)diphenylmethyl]-pyridine,
2-bromo-5-[(3-bromophenyl)diphenylmethyl]-pyridine,
2-bromo-5-[tris-(3-fluorophenyl)methyl]-pyridine,
2-bromo-5-[(3-ethylphenyl)diphenylmethyl]-pyridine,
2-bromo-5-[bis(3-fluorophenyl)phenylmethyl]-pyridine,
2-bromo-5-[(3-propoxyphenyl)diphenylmethyl]-pyridine,
2-bromo-5-[tris-(3-trifluoromethylphenyl)methyl]-pyridine,
2-bromo-3-ethyl-5-[(3-methylphenyl)diphenylmethyl]-pyridine,
2-bromo-5-[(2-chlorophenyl)diphenylmethyl]-pyridine,
2-bromo-5-[(2-isopropylphenyl)diphenylmethyl]-pyridine,
2-bromo-5-[bis-(2-fluorophenyl)phenylmethyl]-pyridine,
2-bromo-5-[tris-(2-methylphenyl)methyl]-pyridine,
2-bromo-5-[(2-ethoxyphenyl)diphenylmethyl]-pyridine,
2-bromo-5-[(2-trifluoromethylphenyl)diphenylmethyl]-pyridine, and
2-bromo-5[(2-chlorophenyl)phenylmethyl]-pyridine

to obtain thereby the corresponding R-substituted-5-(R_1-substituted)-picolinic acid such as for example:

3-methyl-5-(triphenylmethyl)-picolinic acid (m.p. 195—196, 5°C),
5-[(4-biphenyl)diphenylmethyl]-picolinic acid (m.p. 213—214, 5°C),
5-[(2-chlorophenyl)phenylmethyl]-picolinic acid (m.p. 197—200°C).

EXAMPLE 2

5-(Diphenylmethyl)-Picolinic Acid

A. 5-(diphenylmethyl)-2-pyridine

To a mixture of 92.1 g (0.5 mole) of benzhydrol and 142.7 g. (1.5 mole) of 2-hydroxypyridine heated at 180°, add with stirring 1.5 ml. of concentrated sulfuric acid. Heat the mixture at 250—255 for 2 hours with the removal of water. Pour the cooled reaction mixture into water, stir, and extract with chloroform. Concentrate the chloroform extracts to a residue containing 5-(diphenylmethyl)-2-pyridone. Triturate the residue with ethyl acetate and filter the solids to obtain 5-(diphenylmethyl)-2-

pyridone plus other isomers. Recrystallize from acetonitrile to obtain the product of this example, m.p. 174°—176°C.

B. 2-Chloro-5-(Diphenylmethyl)-Pyridine

Heat 55 g. of the crude 5-(diphenylmethyl)-2-pyridone and 110 ml. of phenylphosphonic dichloride at 200°—210° with stirring for 6 hours. Pour the cooled reaction mixture onto ice, basify with ammonium hydroxide, extract with ethyl ether, dry the ether extracts, and concentrate to a residue. Distill the residue at 160°—175°/0.15 mm. and crystallize the distillate from hexane to obtain 2-chloro-5-(diphenylmethyl)-pyridine, m.p. 69.5—71°.

C. 5-(Diphenylmethyl)-Picolinic Acid

Heat a mixture of 16.5 g. (.059 mole) of 2-chloro-5-(diphenylmethyl)-pyridine and 10.6 g. (0.059 mole) of cuprous cyanide in 120 ml. of hexamethylphosphoramide with stirring at 210°—220°C for 7 hours. Pour the cooled reaction mixture into a solution of 200 ml. of ethylenediamine in 500 ml. of water, and extract with benzene. Wash with benzene extracts with 10% aqueous sodium cyanide, then with water, dry, treat with activated charcoal, filter, and concentrate to obtain 2-cyano-5-(diphenylmethyl)-pyridine. This compound is converted directly to the title compound by heating at reflux with 13 g. of potassium hydroxide pellets in 100 ml. water and 200 ml. ethylene glycol for 15 hours. Remove the ethylene glycol and water under reduced pressure, dissolve the residue in water, acidify with concentrated hydrochloric acid, and extract with chloroform. Dry the chloroform extracts. Concentrate the dried extracts to a residue and triturate the residue with isopropyl ether. Filter the solids, dry and recrystallize from ethanol to obtain 5-(diphenylmethyl)-picolinic acid, m.p. 189—191°C.

In a similar manner, subject an equivalent quantity of the following 2-chloro-(R_1-substituted diphenylmethyl)-pyridines (which can be prepared as described in step A and B of this example) to the process of the foregoing step to obtain thereby the corresponding (R_1-substituted diphenylmethyl)-picolinic acids:

2-chloro-5-(2-chlorophenyl-phenylmethyl)-pyridine,
2-chloro-5-[bis-(4-fluorophenyl)-methyl]pyridine,
2-chloro-5-(4-biphenyl-phenylmethyl)-pyridine,
2-chloro-5-[4-trifluoromethyl)-phenyl-phenylmethyl]-pyridine,
2-chloro-5-(3-methoxyphenyl-phenylmethyl)-pyridine,
2-chloro-5-[bis-(4-methylphenyl)-methyl]-pyridine, and
2-chloro-5-(diphenylmethyl)-3-methylpyridine.

EXAMPLE 3

5-(4-Chlorophenyl-Phenylmethyl)-Picolinic Acid

A. 5-(4-Chlorophenyl-Phenylmethyl)-2-Pyridone

Combine 109.3 g. (0.5 mole) of 4-chlorobenzhydrol with 142.7 g. (1.5 mole) of 2-hydroxypyridine and heat at 150°C with stirring until molten. Add about 2 ml. of concentrated sulfuric acid and continue heating to 240—250°C while removing water from the reaction mixture. Permit the reaction to continue for about 2 hours, then cool the reaction mixture to about 25°C. Treat the resulting solid with ethyl acetate and water and filter to remove the undesired 3-(4-chlorophenyl-phenylmethyl)-2-pyridone. The organic layer is separated and washed with water several times and dried over potassium carbonate and filtered. Concentrate the filtrate to half volume and filter to remove the remaining 3-substituted-2-pyridone. Evaporate the filtrate and dissolve the residue in ethyl ether. Upon standing overnight the 5-(4-chlorophenyl-phenylmethyl)-2-pyridone crystallizes, yield 60 g., m.p. 164°—169°C.

B. 2-Chloro-5-(4-Chlorophenyl-Phenylmethyl)-Pyridine

Combine 50 g. (.174 mole) of the 5-substituted 2-pyridone from step A with 125 ml. of phenylphosphonic dichloride and heat at 210°—220°C for about 7 hours with stirring. Allow to stand overnight and pour onto ice. Basify with ammonium hydroxide and extract with ethyl ether. Dry the ether solution and concentrate to a residue. Distill the residue and collect the fraction boiling at 205°—215°C at 0.55 mm. (49 g.).

C. 5-(4-Chlorophenyl-Phenylmethyl)-Picolinic Acid

Dissolve 55 g. of the product of step B in 200 ml. of dry hexamethylphosphoramide and add 32 g. (.36 mole) of cuprous cyanide. Heat the reaction mixture at 210°—220°C for 7 hours. Pour the reaction mixture into about 500 ml. of ice water containing 200 ml. of ethylenediamine and extract with benzene. Wash the benzene

extract with 10% sodium cyanide solution then with water. Treat the benzene solution with activated charcoal and filter through a suitable filter aid. Evaporate the filtrate to dryness, dissolve the residue in 300 ml. of ethylene glycol and add 20 g. of potassium hydroxide dissolved in 100 ml. of water. Reflux the reaction mixture overnight and remove the solvent *in vacuo*. Dissolve the residue in water, treat with activated charcoal and filter. Acidify the filtrate with concentrated hydrochloric acid, extract the precipitate thus formed with chloroform and evaporate the extract to a residue. Triturate the residue with acetonitrile and obtain thereby the product of this example, m.p. 200°—203°C.

EXAMPLE 4

3,5-Bis-(Diphenylmethyl)-Picolinic Acid

A. N-Diphenylmethyl-2-pyridone

Combine 92.1 g (0.5 mole) of benzhydrol with 142.7 g. (1.5 mole) of 2-hydroxypyridine and heat to 190°C with stirring. Add 1.5 ml. of concentrated sulfuric acid and follow the procedure of Example 3, step A to obtain thereby the product of this step, yield 68 g., m.p. 142°—145°C.

B. 3,5-Bis-(Diphenylmethyl)-2-pyridone

Combine 46 g. (.18 mole) of N-substituted-2-pyridone with 33.2 g. (.18 mole) of benzhydrol and heat to 230°C. Add about 1 ml. of concentrated sulfuric acid and heat at 250°—260°C for about 2 hours. Cool the reaction mixture to about 25°C and stir the solid reaction product with hot acetonitrile, filter, wash and dry to obtain thereby the product of this step, yield 49 g., m.p. about 240°C.

C. 2-Chloro-3,5-bis-(diphenylmethyl)-pyridine

Combine 49.5 g. (0.11 moles) of 3,5-bis-(diphenylmethyl)-2-pyridone (prepared as described in step B) with 105 ml. of phenylphosphonic dichloride and heat the reaction mixture with stirring at 200°—210°C for 6 hours. Pour the reaction mixture onto ice and basify with ammonium hydroxide. Extract with ethyl ether, dry the extract and evaporate to yield a residue which is crystallized from ethanol to yield the product of this step, yield about 40 g., m.p. 131°—133°C.

D. 3,5-Bis-(Diphenylmethyl)-Picolinic Acid

Combine 38.4 g. (.086 mole) of 2-chloro-3,5-bis-(diphenylmethyl)-pyridine (as prepared in step C) with 15.3 g. (0.17 mole) of cuprous cyanide in 180 ml. of dry hexamethyl-phosphoramide. Heat the reaction mixture at 210°—220°C for 7 hours. Pour the reaction mixture into aqueous ethylenediamine, extract with benzene, wash the benzene extracts with 10% sodium cyanide then with water and dry over potassium carbonate. Filter and concentrate the filtrate to a residue. Dissolve the residue in 300 ml. of ethylene glycol, add a solution of 15 g. potassium hydroxide in 90 ml. of water and reflux for about 22 hours. Concentrate the reaction mixture to a residue *in vacuo* and acidify the residue with dilute hydrochloric acid. Extract with benzene, and concentrate the solution to a residue containing the title product which was purified by conversion to the diethanolamine salt followed by regeneration of the acid, m.p. 172°—175°C.

In a similar manner, subject an equivalent quantity of the following 2-chloro-3,5-bis-(R_1-substituted diphenylmethyl)-pyridines (which can be prepared according to steps A to C of this example) to the process set forth above to obtain thereby the corresponding 3,5-bis-(R_1-substituted diphenylmethyl)-picolinic acids:

2-chloro-3,5-bis-(4-chlorophenyl-phenylmethyl)-pyridine,
2-chloro-3,5-bis-[bis-(4-chlorophenyl)-methyl]-pyridine,
2-chloro-3,5-bis-(2-chlorophenyl-phenylmethyl)-pyridine,
2-chloro-3,5-bis-[bis-(4-fluorophenyl)-methyl]-pyridine,
2-chloro-3,5-bis-(4-biphenyl-phenylmethyl)-pyridine,
2-chloro-3,5-bis-[4-trifluoromethylphenyl-phenylmethyl]-pyridine,
2-chloro-3,5-bis-(3-methoxyphenyl-phenylmethyl)-pyridine, and
2-chloro-3,5-bis-[bis-(4-methylphenyl)-methyl]-pyridine.

EXAMPLE 5

5-[Bis-(4-Chlorophenyl)-methyl]-Picolinic Acid

A. 5-[Bis-(4-Chlorophenyl)-Methyl]-2-Pyridone

Combine 50.6 g. (0.2 mole) of 4,4′-dichlorobenzhydrol with 57.1 g. (.6 mole) of 2-hydroxy pyridine, with stirring heat to 200 C and add dropwise 1.0 ml. of concentrated sulfuric acid. Increase the reaction temperature to 240°C—250°C and maintain at that temperature range while collecting water emanating from the reaction. Cool the

reaction mixture, add a mixture of ethyl acetate and water with stirring and separate the liquid phases. Dry the organic phase, reduce the volume of ethyl acetate, cool to precipitate the crude product, yield 43 g. Crystallization from ethanol affords the product of this step, m.p. 211°—215°C.

B. 2-Chloro-5-[Bis-(4-Chlorophenyl)-Methyl]-Pyridine

To a mixture of 35.2 g. (.11 mole) of 5-[bis-(4-chlorophenyl)-methyl]-2-pyridone and 11.8 g. (.11 mole) of 2,4-lutidine, add 50.6 g. (.33 mole) of phosphorous oxychloride (dropwise) while heating the reaction mixture at 80°. Then, heat the reaction mixture at 120°C for six hours. Pour the reaction mixture onto ice, basify with ammonium hydroxide, extract with benzene and remove both the benzene and residual 2,4-lutidine by distillation. Distill the residue at about 195—210°C (.01 mm) to obtain thereby about 30 g. of the product of this step as a yellow viscous oil.

C. 5-[Bis-(4-Chlorophenyl)-Methyl]-Picolinic Acid

Dissolve the product of step B above in about 150 ml. of dry hexamethylphosphoramide, add 15.4 g. (.172 mole) of cuprous cyanide and follow the procedure described in Example 4, step D to obtain the product of this example.

EXAMPLE 6

5-(Triphenylmethyl)-Picolinamide

Dissolve 5 g. of 5-(triphenylmethyl)-2-cyanopyridine in a mixture consisting of 50 ml. of water and 1.0 liter of methanol. Add 4 g. of potassium hydroxide and heat the mixture at reflux for fifteen (15) hours. Remove the methanol under reduced pressure, triturate the residue with water and dry the solids obtained thereby. Crystallize the product from acetonitrile to obtain the product of this example, m.p. 239°—240°C.

EXAMPLE 7

4-(Diphenylmethyl)-Picolinic Acid

A. 4-(Diphenylmethyl)-Picolinamide

Dissolve 20 g. (0.082 mole) of 4-benzhydrylpyridine in 200 ml. of formamide and, with external cooling, add 4.35 ml. (0.082 mole) of sulfuric acid. Adjust the reaction temperature to 5°—10°C while adding 21.6 g. (0.24 mole) of t-butyl hydroperoxide and 67 g. (0.24 mole) of ferrous sulfate over a 30 minute interval. Remove the iron salts by filtration. Wash the precipitate with chloroform and water and separate the two liquid phases. Extract the aqueous phase with chloroform, wash the combined chloroform phases with water and dry. Concentrate the extract to a residue, dissolve the residue in ether, filter and obtain the product of this step from the ether solution, yield 3.5 g., m.p. 165°—170°C. Additional product may be obtained by extracting the iron salts with refluxing chloroform.

B. 4-(Diphenylmethyl)-Picolinic Acid

Dissolve 5.3 g. of 4-(diphenylmethyl)-picolinamide (prepared in step A) in 80 ml. of concentrated hydrochloric acid and heat to reflux. Continue to reflux the reaction mixture overnight. Remove 50 ml. of the solvent by distillation *in vacuo*, treat the residue with ice and basify with excess 10% sodium hydroxide. Add 300 ml. of water and extract the solution with 50 ml. of ethyl ether. Adjust the pH of the aqueous phase to about 5, recover the precipitate by filtration and dry to obtain thereby the product of this example, m.p. 172°—177°C. Crystallize the product from 75 ml. of acetonitrile, yield 3.8 g., m.p. 176°—178°C.

In a similar manner, subject an equivalent quantity of the following 4-(R_1-substituted diphenylmethyl)-picolinamides (which can be obtained according to step A of this example) to the process set forth above to obtain thereby the corresponding 4-(R_1-substituted diphenylmethyl)-picolinic acids:

4-(4-chlorophenyl-phenylmethyl)-picolinamide,
4-[bis-(4-chlorophenyl)-methyl]-picolinamide,
4-(2-chlorophenyl-phenylmethyl)-picolinamide,
4-(4-biphenyl-phenylmethyl)-picolinamide,
4-(4-Trifluoromethylphenyl-phenylmethyl)-picolinamide,
4-(3-methoxyphenyl-phenylmethyl)-picolinamide, and
4-[bis-(4-methylphenyl)-methyl]-picolinamide.

EXAMPLE 8

4-(1,1-Diphenylpropyl)-Picolinic Acid

A. 4-(1,1-Diphenylpropyl)-Pyridine

Dissolve 2.5 g. of sodium in 500 ml. of liquid ammonia in the presence of a catalytic amount of ferric nitrate. Add dropwise to the resulting suspension over a 20 minute interval a solution containing 24.5 g. of 4-diphenylmethyl pyridine in 600 ml of ether. Stir the resulting dark red mixture for an additional 20 minutes, then add 13 g. of ethyl bromide dropwise. Add an additional 500 ml. of ammonia, stir overnight, then add 300 ml. of ether followed by 150 ml. of water. Separate the solvent layers. Wash the ether layer with water until neutral, dry and remove the solvent under reduced pressure to a residue. Distill the residue at 192°—200°C/1.6 to 2 mm. and obtain thereby 14.7 g. of the title compound as an orange colored oil.

B. 4-(1,1-Diphenylpropyl)-Picolinamide

Subject the 4-(1,1-diphenylpropyl)-pyridine prepared in step A to the process of Example 7, step A and obtain thereby 13.9 of a yellow oil which may be crystallized from acetonitrile to yield the title product, m.p. 144°—147°C.

C. 4-(1,1-Diphenylpropyl)-Picolinic Acid

Dissolve 3.8 g. of 4-(1,1-diphenylpropyl)-picolinamide in 50 ml. of ethanol, add 100 ml. of 10% aqueous potassium hydroxide and heat the resulting mixture at reflux overnight. Remove the ethanol under reduced pressure, add water to the residue and adjust to about pH 5 with 10% aqueous hydrochloric acid. Filter the resulting solid and crystallize the precipitate from ethanol to obtain thereby the compound of this example, yield 1.6 g., m.p. 191°—193°C.

EXAMPLE 9

Glyceryl (5-Triphenylmethyl)-Picolinate

A. β-γ-Isopropylidenedioxypropyl (5-triphenylmethyl)-picolinate

Heat with stirring on a steam bath for 1 1/2 hours a mixture of 4 g of cyanomethyl 5-(triphenylmethyl)-picolinate, 50 ml. of 2,2-dimethyl-1,3-dioxolane-4-methanol and 2 ml. of triethylamine. Treat the reaction mixture with water, cool and filter to yield the product of this step.

B. Glyceryl 5-(Triphenylmethyl)-Picolinate

Heat with stirring on a steam bath for one hour a mixture of 4.5 g of β-γ-isopropylidenedioxypropyl 5-(triphenylmethyl)-picolinate and 90 ml. of 75% acetic acid. Pour the reaction mixture onto ice. Filter and dissolve the resulting solid in ethyl acetate, wash twice with water, dry over $MgSO_4$ and concentrate, recrystallize from acetonitrile m.p. 183—186° to obtain thereby, the product of this Example.

EXAMPLE 10

5-(Triphenylmethyl)-Picolinic Acid Diethanolamine Salt

Combine 5.5 g. of 5-(triphenylmethyl)-picolinic acid and 1.6 g. of diethanolamine in 200 ml. of ethanol and heat to form a solution, then cool to precipitate the salt. Recrystallize from ethanol to give the title compound, m.p. 206—209°.

EXAMPLE 11

5-(4-Chlorophenyl-Phenylmethyl)-Picolinic Acid Diethanolamine Salt

Combine 0.97 g. of 5-(4-chlorophenyl)-phenylmethyl)-picolinic acid (see Example 3C with 0.4 g. of diethanolamine in 100 ml. of ethyl acetate. Heat the reaction mixture and decant solvent from the brown insoluble residue. Upon standing, the product of this example precipitates from the ethyl acetate solution, m.p. 108°—115°C.

EXAMPLE 12

5-[Bis-(4-Chlorophenyl)-Methyl]-Picolinic Acid Piperazine Salt

Combine 19.8 g. (.055 mole) of 5-[bis-(4-chlorophenyl)methyl]-picolinic acid with 4.7 g. of piperazine in hot methanol. Add 5 volumes of ether and collect the precipitate by filtration. Recrystallize the precipitate from ethanol to obtain thereby the product of this example, m.p. 240°—255°C.

EXAMPLE 13

Cyanomethyl 5-(Triphenylmethyl)-Picolinate

To a stirred mixture of 5 g. 5-(triphenylmethyl)-picolinic acid and 6.1 g. triethyl amine in 150 ml. acetone add 4.5 g. of chloroacetonitrile. Heat the resulting mixture

at reflux 15 hr., cool, filter. Concentrate the filtrate to a residue and triturate residue with water, dry. Recrystallize twice from isopropyl ether-ethanol to obtain the product of this example, m.p. 173°—175°.

EXAMPLE 14

Cyanomethyl 5-(Diphenylmethyl)-picolinate

Suspend 4.3 g. (.015 mole) of 5-(diphenylmethyl)-picolinic acid in 100 ml. of acetone with stirring and add 2.3 g. (.023 mole) of triethylamine. To the resulting solution add dropwise 1.7 g. (.023 mole) of chloroacetonitrile. Stir the reaction mixture at room temperature (25°C) for 15 minutes, then reflux for 4 hours. Cool and filter the reaction mixture. Concentrate the filtrate to a residue *in vacuo* and triturate the residue with hot isopropyl ether to yield the product of this example, yield 3.5 g., m.p. 95°—98°C.

EXAMPLE 15

Methyl 5-(Triphenylmethyl)-Picolinate

Heat at reflux 4 gm. (0.01 mole) of cyanomethyl-5-(triphenylmethyl)picolinate and 2 ml. of triethylamine in 50 ml. methanol for 4 hr. Remove methanol under reduced pressure. Triturate solid residue with water and recrystallize from ethylacetate-isopropyl ether, to obtain the product of this example, m.p. 160°—164°.

In a similar manner by substituting other alcohols, such as ethanol, propanol, isopropanol, *n*-butanol or alcohols of the general formula HO—alkylene—NR$_1$R$_2$ for methanol, and by following the process of this example 15 the corresponding esters may be prepared (e.g. 5-(triphenylmethyl)-picolinic acid isopropyl ester, m.p. 170—182°C).

EXAMPLE 16

N,N-Diethyl-5-(Triphenylmethyl)-Picolinamide

Heat at reflux for 6 hours a mixture of 0.1 mole of cyanomethyl-5-(triphenylmethyl)-picolinate and 0.5 moles of diethylamine. Cool the reaction mixture, pour into water and extract with chloroform. Dry the chloroform layer over anhydrous sodium sulfate and evaporate to obtain thereby the product of this example.

In a similar manner, by substituting an equivalent quantity of other mono or di-alkylamines or mono or dialcoholamines or heterocyclic amines, such as methylamine, ethylamine, octylamine, dodecylamine, ethanolamine, diethanolamine, piperazine, morpholine, pyrrolidine or piperidine and by following the process set forth in this example 16 the corresponding mono or di-alkylamides may be prepared.

EXAMPLE 17

5-(Triphenylmethyl)-Picolinic Acid

A. 5-(triphenylmethyl)-5-cyanopentanone-2

To a solution of 28.3 g. (0.1 M.) of triphenylmethyl acetonitrile in 50 ml. of MeOH there was added 0.5 ml. of a 2N methanolic solution of sodium methoxide. To the stirred, cooled solution there was added 3.5 g. (0.05 M.) of methyl vinyl ketone. After standing overnight at room temperature, 100 ml. of ether was added and the ethereal solution was washed successively with 10% acetic acid, water, 5% sodium bicarbonate solution and water. The ether layer was dried and concentrated. The excess triphenylmethyl acetonitrile was removed leaving the compound of this example as a viscous oil.

B. 2-methyl-5-triphenylmethyl piperidine

10 g. of 5-(triphenylmethyl)-5-cyanopentanone-2 and 100 ml. of ethanol and 2 g. of Raney Nickel catalyst was hydrogenated at 75—80° at 800 p.s.i. until the theoretical uptake of hydrogen was observed. The reaction mixture was filtered and concentrated *in vacuo* to yield the product of this example as a crystalline solid.

C. 5-(triphenylmethyl)-2-methylpyridine

To a solution of 12 g. of 5-triphenylmethyl-2-methyl piperidine and 100 ml. of p-cymene there was added 10 g. of 5% palladium on charcoal catalyst. The mixture was refluxed for 12 hours, cooled, filtered and the p-cymene removed *in vacuo*. The residual product crystallized on trituration with hexane.

D. 5-(triphenylmethyl)-picolinic acid

To a solution of 1.4 g. of selenium dioxide in 15 ml. of pyridine containing 4% water, there was added 3.3 g. of 5-triphenylmethyl-2-methyl pyridine in 30 ml. of pyridine. The reaction mixture was refluxed for four hours, filtered hot and on cooling the product of this example crystallized (m.p. 215—217°C.).

EXAMPLE 18

5-(Diphenylmethyl)-Picolinic Acid

A. 6,6-diphenyl-5-cyano-hexane-2-one

To a solution of 20.7 g. (0.1 M) of 3,3-diphenyl propionitrile in 50 ml. of methanol there was added 0.5 ml. of a 2*N*-methanolic solution of sodium methoxide. To the stirred, cooled solution there was added 3.5 g. (0.05 M) of methyl vinyl ketone. After standing overnight at room temperature, 100 ml. of ether was added and the ethereal solution was washed successively with 10% acetic acid, water, 5% sodium bicarbonate solution, and water. The ether layer was dried and concentrated. The excess 3,3-diphenylpropionitrile was removed, leaving the compound of this example as a viscous oil.

B. 2-methyl-5-(diphenylmethyl)-piperidine

A mixture of 10 g. of 6,6-diphenyl-5-cyanohexane-2-one, 100 ml. of ethanol and 2 g. of Raney Nickel was hydrogenated at 75—80° at 800 p.s.i. until the theoretical uptake of hydrogen was complete. The reaction mixture was filtered and concentrated *in vacuo* to yield the product of this example as a solid.

C. 2-methyl-5-(diphenylmethyl)-pyridine

Is prepared from the product of the above step B as described in step C of Example 17.

D. 5-(diphenylmethyl)-picolinic acid

To a solution of 1.4 g. of selenium dioxide in 15 ml. pyridine containing 4% water, there was added 2.6 g. of 2-methyl-5-(diphenylmethyl)-pyridine in 30 ml. of pyridine. The reaction mixture was heated at reflux for 4 hours, filtered hot and on cooling the product of this example crystallized (m.p. 189—191°C.).

EXAMPLE 19

5-(Diphenylmethyl)-Picolinic Acid

A. 3-(diphenylmethyl)-pyridine-N-oxide

To a solution of 22 g. (.09M) of 3-(diphenylmethyl)-pyridine in 70 ml. acetic acid is added 14 ml. of 30% hydrogen peroxide. The solution is heated at 70—80° for 15 hours, the acetic acid is reduced *in vacuo* to about 1/3 the volume, water is added, the solution is basified with sodium hydroxide, extracted with methylene chloride, dried and concentrated to give the product of this example as a solid.

B. 3-(diphenylmethyl)-1-methoxypyridinium methylsulfate

To a solution of 25 g. of 3-(diphenylmethyl)-pyridine-N-oxide in 160 ml. benzene is added dropwise 11.4 g. of dimethylsulfate. The solution is heated at reflux for 4 hours. The mixture is cooled, and the benzene is decanted from the product of this reaction which separates as an oil.

C. 2-cyano-5-(diphenylmethyl)-pyridine

A solution of the crude product of the above example in 80 ml. of water is added dropwise to a solution of 13.2 g. of sodium cyanide in 80 ml. of water, which is maintained at 0°. The mixture is stirred one hour. The aqueous solution is decanted from a semi solid residue. To this residue is added water, and the mixture is extracted with chloroform. The chloroform solution is dried and concentrated, giving a solid which is a mixture of isomers. The desired product of this example is obtained by fractional crystallization.

D. 5-(diphenylmethyl) picolinic acid

Is prepared from the product of the above step C as described in Example 1 step B (m.p. 189—191°C.).

EXAMPLE 20

5-(Triphenylmethyl)-Picolinic Acid

A. 3-tritylpyridine-1-oxide

26.0 g. (0.081 mole) of 3-tritylpyridine is dissolved in 200 ml. of glacial acetic acid and treated with 20 ml. 30% hydrogen peroxide. The solution is refluxed 16 hours, cooled and diluted with water, the white crystalline solid collected and dissolved in chloroform. The chloroform solution is shaken with dilute sodium hydroxide, washed with water, dried and concentrated to a white solid. Recrystallization from absolute ethanol affords the pure 1-oxide; m.p. 290—292°.

B. 1-methoxy-3-tritylpyridinium methyl sulfate

22.0 g. of 3-tritylpyridine-1-oxide is dissolved in 350 ml. toluene and treated with 9.0 g. dimethyl sulfate. The solution is refluxed for 2.5 hours, during which period an oil separates which crystallizes upon cooling; m.p. 162—165°. Recrystallization from acetonitrile/ether yields the pure methyl sulfate; m.p. 169—171°.

C. 2-cyano-5-tritylpyridine

25.0 g. of 1-methoxy-3-tritylpyridinium methyl sulfate is dissolved in 800 ml. water and added dropwise with stirring to an ice-cooled solution of 13.5 g. of sodium cyanide in 100 ml. water while bubbling a rapid stream of nitrogen through the mixture. After 4 hours at ambient the precipitated white solid is filtered and recrystallized from methanol to yield the pure 2-cyano-5-tritylpyridine; m.p. 180—182°.

D. 5-(triphenylmethyl)-picolinic acid

Is prepared from the product of the above step C as described in Example 1 step B (m.p. 215—217°C).

EXAMPLE 21

5-(triphenylmethyl)-Picolinic Acid

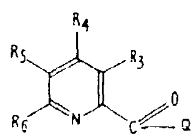
A mixture of 8.2 g. 2-styryl-5-(triphenylmethyl)-pyridine and 120 ml. of acetone is cooled to −10°C and with vigorous stirring 6.66 g. of finely divided potassium permanganate is added slowly, in a portion-wise fashion, over a 1.5 hour period whilst maintaining the temperature below −5°C. Allow the mixture to stand at −15°C for 15 hours, filter and wash the solids with chloroform and extract three times with 150 ml. of boiling water. Acidify the aqueous extracts with hydrochloric acid and extract with ether. Discard the ether extracts and basify the aqueous phase to pH 2.5 and filter and dry the precipitated acid which is recrystallized from benzene to yield the title product (m.p. 215—217°C).

EXAMPLE 22

18 g. 2-methyl-5-(triphenylmethyl) pyridine, 1 liter of water, 9 g. of potassium-permanganate are heated on a steam bath for about 3 hours until the reaction mixture is colorless. 9 g. of potassiumpermanganate, 200 milliliters of water are added and the reaction mixture is heated for about 5 hours until colorless. Filter and wash thoroughly with hot water (70—90°C), combine the filtrate and washes, cool to about 25°C, acidify with hydrochloric acid, and recover the 5-(triphenylmethyl) picolinic acid by filtration (m.p. 215—217°C).

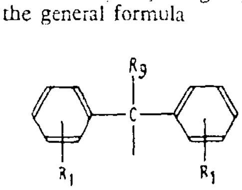
WHAT WE CLAIM IS:—

1) A picolinic acid derivative of the general formula



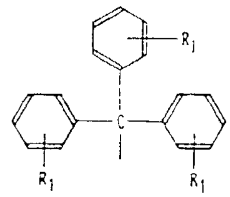
(I)

or a pharmaceutically acceptable salt thereof, wherein Q is hydroxy, alkoxy, cyanoalkoxy, glyceryloxy, —NR_7R_8, —O—alkylene—NR_7R_8 or —NR_7—alkylene—OH; R_7 and R_8 which may be the same or different are hydrogen or alkyl or R_7 and R_8 together with the amido nitrogen atom may form a 5 to 7 membered heterocyclic ring which may contain a second heteroatom, being oxygen or nitrogen; R_5 is hydrogen, a diphenylmethyl group of the general formula



(II)

or a triphenylmethyl group of the general formula



(III)

wherein R_1 is hydrogen, halogen, hydroxy, alkyl, alkoxy, trifluoromethyl or phenyl and R_6 is hydrogen or lower alkyl; provided that: when R_5 is hydrogen, R_3 and R_6 are hydrogen and R_4 is a diphenylmethyl group of the general formula (II) defined above; and when R_5 is the diphenylmethyl group (II), R_4 and R_6 are hydrogen and R_3 is hydrogen, lower alkyl or a diphenylmethyl group of the general formula (II) defined above; and when R_5 is the triphenylmethyl group (III), R_3, R_4 and R_6 are hydrogen or one of R_3, R_4 and R_6 is lower alkyl the other two being hydrogen.

2) A compound according to claim 1, and subject to the provisos stated therein wherein Q is hydroxy, alkoxy, cyanoalkoxy, glyceryloxy or NH_2, said alkyl and alkoxy groups have 1 to 12 carbon atoms; R_5 is hydrogen, a diphenylmethyl group of the general formula II or a triphenylmethyl group of the general formula III, wherein R_1 is hydrogen, halogen, hydroxy, alkyl, alkoxy, said alkyl and alkoxy groups have 1 to 6 carbon atoms, trifluoromethyl or phenyl and R_6 is hydrogen or alkyl containing 1 to 6 carbon atoms.

3) A compound according to claim 1 or 2, wherein Q is hydroxy, alkoxy containing 1 to 3 carbon atoms, OCH_2CN, NH_2 or glyceryloxy, R_1 is hydrogen, halogen or phenyl.

4) A compound according to any one of claims 1 to 3, R_5 is hydrogen, a diphenylmethyl group II or a triphenylmethyl group III, in which groups R_1 is hydrogen, chloro or phenyl; R_6 is hydrogen, methyl or ethyl; and when R_5 is the diphenylmethyl group (II), R_4 and R_6 are hydrogen and R_3 is hydrogen or the diphenylmethyl group of the general formula (II); and when R_5 is the triphenylmethyl group (III), R_3, R_4 and R_6 are hydrogen or one of R_3, R_4 and R_6 is methyl the other two being hydrogen.

5) A compound according to any one of claims 1 to 4, wherein R_1 is hydrogen or chloro.

6) A compound according to any one of claims 1 to 5, wherein Q is hydroxy or isopropoxy, R_5 is a diphenylmethyl group II or a triphenylmethyl group III, in which groups R_1 and R_6 are hydrogen, and when R_5 is the diphenylmethyl group, R_4 and R_6 are hydrogen and R_3 is hydrogen or the diphenylmethyl group II, and when R_5 is the triphenylmethyl group (III), R_3, R_4 and R_6 are hydrogen.

7) 5-Tritylpicolinic acid or a salt thereof.

8) 5-[α-(4-Chlorophenyl)-benzyl]-picolinic acid or a salt thereof.

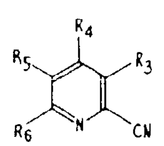
9) 5-Triphenylmethyl-picolinic acid cyanomethyl ester.

10) 5-Triphenylmethyl picolinic acid methyl or glycerol ester.

11) Compound according to any one of claims 1 to 9, being in the form of the diethanolamine salt.

12) A process for the preparation of a picolinic acid derivative of the general formula I set forth in any one of claims 1 to 11, which process comprises one of the following processes (a) to (f):

a) hydrolysis of a 2-cyanopyridine of the general formula (V)



(V)

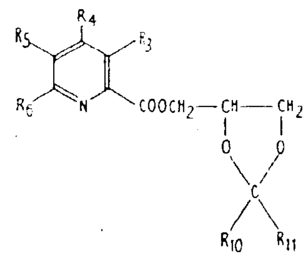
wherein R_3, R_4, R_5 and R_6 are as defined above, to form the corresponding acid of formula (I), wherein Q is hydroxy and R_3, R_4, R_5 and R_6 are as defined above;

b) hydrolysis under mild conditions of a 2-cyanopyridine of the general formula (V) as defined above, to form the corresponding acid of formula (I), wherein Q is NH_2 and R_3, R_4, R_5 and R_6 are as defined above;

c) for the preparation of compounds of formula (I), wherein R_4 is a diphenylmethyl group of formula (II) and Q is NH_2, reaction of a corresponding 4-benzhydrylpyridinium sulfate salt or 4-benzhydrylpyridine in the presence

of sulfuric acid with formamide in the presence of ferrous sulfate and a peroxide.

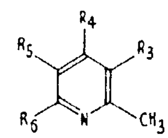
d) hydrolysis of an alkylidenedioxypropylester of a picolinic acid of the general formula (XV)



(XV),

wherein R_3, R_4, R_5 and R_6 are defined as above and R_{10} and R_{11} are lower alkyl, to form the corresponding glycerylester;

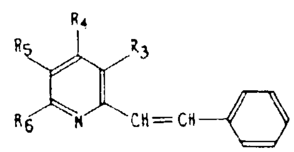
e) oxidation of a 2-methylpyridine of the general formula (XVI)



(XVI),

wherein R_3, R_4, R_5 and R_6 are as defined above, to form the corresponding picolinic acid;

f) oxidation of a 2-styrylpyridine of formula (XVII)



(XVII),

wherein R_3, R_4, R_5 and R_6 are defined as above, to form the corresponding picolinic acid;

said process selected from the processes a to f being followed if desired by one or more of the following after treatments (i) to (vi):

i) transformation of the compound (I) into its salt;

ii) setting free the compound (I) from its salt;

iii) conversion of a compound (I), wherein Q is hydroxy into the compound (I), wherein Q is alkoxy, cyanoalkoxy, glyceryloxy or —O—alkylene—NR_7R_8.

iv) conversion of a compound (I), wherein Q is cyanoalkoxy (the alkoxy group containing up to 6 carbon atoms), wherein the cyano group is attached to the C-atom of position 1 (i.e.

$$-O-\underset{}{\overset{\overset{\displaystyle CN}{|}}{CH}}$$

alkyl), preferably cyanomethoxy into a compound of formula (I), wherein Q is alkoxy, —NR_7R_8, —O—alkylene—NR_7R_8 or —NR_7—alkylene—OH;

v) conversion of a compound of formula (I), wherein Q is hydroxy into a compound of formula (I), wherein Q is —NR_7R_8;

vi) conversion of a compound of formula (I), wherein Q is other than hydroxy, especially NR_7R_8, preferably NH_2 by hydrolysis under preferably acidic conditions, into a compound (I), wherein Q is hydroxy.

13) A process for the preparation of a compound as claimed in any one of claims 1 to 11 substantially as hereinbefore described.

14) A picolinic acid derivative of the general formula (I) and its salts set forth

in any one of claims 1 to 11, whenever obtained by a process as claimed in claim 12 or 13.

15) A pharmaceutical composition comprising as active ingredient a compound as claimed in any one of claims 1 to 11 and 14 in association with a suitable pharmaceutical carrier.

16) A process for the preparation of a pharmaceutical composition which comprises bringing a compound as claimed in any one of claims 1 to 11 and 14 into a form suitable for therapeutic administration.

17) A process as claimed in claim 16, wherein the said compound is admixed with a suitable pharmaceutical carrier.

18) A pharmaceutical composition whenever prepared by a process as claimed in claim 16 or 17.

19) A pharmaceutical composition as claimed in claim 15 or 18 in shaped dosage form.

20) A pharmaceutical composition as claimed in claim 15 and substantially as hereinbefore described.

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10 Fleet Street,
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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.